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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/894,967	06/27/2001	William Michael Kavanaugh	02307K-059110US	4693

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EXAMINER
KAUFMAN, CLAIRE M

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/894,967	KAVANAUGH ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The preliminary amendment filed 1/30/02 has been entered.

Sequences

This application contains sequence disclosures that are encompassed by the definitions for nucleic and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.822 (MPEP § 2423):

> (d) *Representation of amino acids.* (1) The amino acids in a protein or peptide sequence shall be listed using the three-letter abbreviation with the first letter as an upper case character, as in WIPO Standard ST.25 (1998), Appendix 2, Table 3.

Otherwise, all bases or amino acids not appearing in WIPO Standard ST.25 (1998), Appendix 2, Table 1 or 3 must be listed in a given sequence as "n" or "**Xaa**," respectively, with further information given in the Feature section of the "Sequence Listing." See 37 CFR 1.823(b). (MPEP § 2423.01)

Applicants are required to use the three-letter amino acid codes including the use of "Xaa" instead of "X" as appears in, for example, claim 1.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Objections

Claim 17 is objected to because of the following informality: In line 7, "ID-NO" should not have a hyphen.

Claim 8 is objected to because of the following informality: In line 2, "1oo" should be "100".

Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-17 rejected under the judicially created doctrine of double patenting over claims 1-19 of U. S. Patent No. 6,280,964 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows: Claimed is a peptide capable of binding a PTB domain, wherein the peptide is 21-100 amino acids in length and comprises one of the listed core sequences encompasses a peptide capable of binding a PTB domain, wherein patented is the peptide is 21-50 amino acids in length and comprises one of the same core sequences. It is note that the listed core sequences are 21 amino acids long and there are no limitations on the 50 amino acids that differ in the pending and patented claims.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10, 13 and 17 and dependent claims 9, 11, 12, 14-16 and 18-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, 10, 13 and 17 are indefinite because it is unclear is "N" in the core sequence is supposed to represent a nitrogen or Asn. Adherence to the requirements of 37 CFR 1.821-1.825 should obviate this rejection.

Claims 1 and are 8 indefinite for reciting "capable of binding" in lines 1-2. It is unclear under what circumstances the peptide is capable of binding, thereby making the metes and bounds of the claims unclear. This rejection could be obviated by replacing "is capable of binding" with "binds".

Claim 13 recites a PTB/phosphorylated ligand interaction . This is confusing, because it seems that the interaction has to occur between a PTB domain, not PTB, and the phosphorylated ligand.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for some peptides having the core sequence disclosed and which **bind** to the specific PTB binding domain having amino acids 1086-1255 of c-erbB2, does not reasonably provide enablement for any amino-acid sequence up to 100 amino acids in length binding to any different phosphotyrosine binding domain. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 1-4, 7 and 22 are to peptides from 5 or 6 to 100 amino acid in length *capable* of binding a PTB domain. Claims 5-6 and 8 are to peptides from 12 or 21 to 100 amino acid in length *capable* of binding a PTB domain. Claim 9 is to a composition, and claims 10-14, 17 and 23-25 are to methods using a peptide and a PTB domain. Applicants provide examples of peptides of 12 amino-acid that **bind** to the PTB domain of the signaling protein SHC (see table 1, page 12). Note that the specification does not teach conditions under which peptides are "capable of binding" and under which they are not, so that the specification does not enable the skilled artisan to use the claimed inventions commensurate in scope with the claims. It is noted that the skilled artisan could, however, use those peptides which bind (not "are capable of") a PTB domain within limits as discussed below.

Kavanaugh et al. (Science 266:1862-1865, 1994) teach a PTB domain from SHC having specificity for binding a pp145 tyrosine phosphorylated protein. This SHC PTB domain is not representative of other PTB domains and is unlike that of any member of the known SH2 domain family, as taught by Kavanaugh et al (see for example page 1864, first column, lines 13-18). While a PTB domain was identified by homology in SCK (see Fig. 4 of Kavanaugh et al., *ibid.)*, no biological function of SCK was known (p. 1864, middle of col. 2). In the specification, the SHC PTB domain was found to bind c-erbB2, but the binding was completely eliminated when c-erbB2 was dephosphorylated, that is, c-erbB2 must be in the tyrosine-phosphorylated form to associate with the PTB domain (p. 11-12, especially p. 11, lines 35-37). Applicants do not provide guidance as of which amino acids besides the 5 or 6 core sequence, and at which position within the 100 amino acid sequence, are involved in the binding either directly or by modifying the secondary or tertiary structure of the peptide. It is well known in the art that it is difficult to predict the functional effects of random single amino acid substitutions, and nearly impossible to predict the functional effects of multiple amino acid substitutions. As up to 95 out of 100 amino-acid mutations are encompassed in the claimed peptides, the claims read on a huge number of possible peptides (at least 2.10^{96}). The examples are of peptides having a

maximum length of 21 amino acids, however, the 100 amino acid limit in the claims is 5 times higher than the examples. The unpredictability of which peptide is capable of binding increases with the size of the peptide. Conditions of binding generally vary according to the length, structure and degree of phosphorylation of the peptide, and the person of skill in the art would not know if the peptide was considered as being "capable of binding" (with which affinity? under which conditions?). While the person skilled in the art would be able to synthesize and screen a large variety of peptides and could produce any one of the 2.10^{96} claimed peptides, it is unpredictable which of these peptides would be enabled as a PTB domain able to bind a known and identified protein, and which peptide (from which up to 95% of the sequence is not defined) would be "capable of binding"(under which binding conditions and with which affinity) a PTB domain (which one, from what protein). Considering the lack of guidance, paucity of examples, the breadth of the claims and the unpredictability as of which peptide would bind to which domain under which conditions, the complex nature of the invention, it would require undue experimentation for the artisan of ordinary skill in the art to make and use the claimed invention commensurate in scope with the claims.

Claims 18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention is drawn to treating a patient suffering from a proliferative cell disorder by administering to the patient an effective amount of the peptide of claim 1. The disorders include atherosclerosis, inflammatory joint disease, psoriasis, restinosis and cancer. However, the specification provides only the most general directions for using the peptide of claim 1 for therapeutic methods that would not enable the skilled artisan and/or physician to practice the methods because of so many unknowns including, for example, which of the peptides encompassed by the claims would inhibit the necessary

PTB interactions in which type of cells. Also, how the peptide could be administered and at what dose so as not to be toxic yet to be effective. What types of inflammatory joint diseases if any could be treated since more than one factor can cause the disease. There are no examples of treatment of any disease. Further, there is no working example of a peptide used to inhibit the function of a particular receptor/SHC interaction in cells *in vitro*, only binding experiments in cell lysates. The experiments presented are not predictive of *in vivo* therapy because they do not reflect the complexities of the intact organism.

The specification draws a simple picture regarding growth factor function such that growth factors generically cause growth and that this growth is mediated only by the newly discovered PTB domain of the SHC protein. Therefore, blocking SCH PTB function in this simple linear pathway will have the desired effect, namely, stopping uncontrolled growth. Nevertheless, the reality is far more complex for many reasons. Growth factors do not merely cause growth, but regulate a variety of cellular functions such as cell differentiation, proliferation and apoptosis. Even for a single growth factor, the cellular environment often makes a difference as to what effect it will have. The second messenger systems that interact with individual growth factors are only partially understood, such that it is not clear how signal specificity is achieved for the large number of growth factors and their numerous receptors and the limited number of signaling systems. It is known that the limited number of intracellular molecules, such as SHC, interact with multiple receptors and other molecules. Intracellular phosphorylation is promiscuous such that in cells a variety of proteins are phosphorylated that can possibly interact with phosphotyrosine binding proteins. Also, many signaling molecules act as part of multi-protein complexes such that it is not predictable what will happen if one component is perturbed. And SHC is only one of many components of a multistep pathway and not even the final effecter in resulting cellular growth such that if the disease mentioned are caused by effects on or by downstream components, the inhibition of SHC interaction with the receptor will have little effect on the proliferative disorder. The state of the prior art serves to highlight how much still needs to be learned about phosphotyrosine binding and the complex nature of PTB domain binding.

The specification provides no guidance as to the specificity of the peptides for the PTB domain, and in fact teaches that these peptides might be used to identify other proteins that contain PTB domains. Whether or not all PTB proteins play a role in these proliferative cell disorders remains to be determined since only one example of a PTB domain protein is provided. There is no assurance that the peptides of the present invention will not interfere with other phosphotyrosine binding proteins other than PTB binding proteins. Even if the peptides were to specifically inhibit the interactions of the SHC PTB domain, it is unpredictable what effect this would have on the intact organisms since signal transduction pathways are known to be redundant, such that blocking one pathway may have little or no effect on the functionings of the intact organisms as demonstrated by knockout experiments with signal transduction proteins.

For the above reasons which include the complex nature of the invention, paucity of guidance, lack of working examples, breadth of the claims as they relate to peptide structure and disease type, lack of information in the prior art and unpredictability of the invention, it would require undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 3, 9-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Dobrusin et al (WO94/07913) .

Dobrusin discloses a peptide (SEQ ID No.7) containing the sequence ENAEpYL which meets the limitation given for the core sequence. Claims 1, 2 and 3 of the instant application are to peptides having a core sequence NX3X1X2X4, which is capable of binding a PTB domain, and SEQ ID NO:7 of Dobrusin et al. has the required structure. Substitution of amino acids such as Leu for Ala ($_{X3}$) are also taught. Claim 9 is

directed to a composition comprising the peptide of claim 1 in a pharmaceutically acceptable carrier. Dobrusin teaches pharmaceutical compositions including compounds of their invention, which include the peptides of instant claim 1 (pages 15-16). Dobrusin teaches that the sequence of the peptides disclosed are derived from sequences in tyrosine kinase receptors, including erbB2/neu n(p. 6, lines 17-24), that include phosphotyrosine and bind other SH2 containing proteins. Also taught is that "The peptides of this invention have been shown to electively inhibit the binding of PLCγ1-SH2(a PTB domain-containing protein) to the EGFR-TK (a tyrosine phosphorylated target) or the abl-SH2 domain to the EGFR" (p. 5, lines 22-25). Also taught is a method of determining if a protein comprises a PTB domain by contacting the protein with a peptide and determining binding wherein the peptide was fused to a detectable label (S^{35}) and bound to protein A-Sepharose beads in a column (a solid support, p. 17, lines 15-30). Additionally the peptides of Dobrusin et al. were used to determine if a test compound was an agonist or antagonist of a PTB/phosphorylated ligand interaction (p. 17-18, *e.g.*, Fig. 3).

Note that while Dobrusin et al. do not report results in the assays for the peptide of SEQ ID NO:7, it appears, absent evidence to the contrary, that all peptides disclosed were tested.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Hazan et al. (Cell Growth Diff. **1, 3,** 1990)

Hazan et al. disclose a fragment of the HER2/neu receptor (a.k.a. c-erbB2), purified by HPLC, that is more than 21 residues long and contains one embodiment of the core sequence recited in the instant claims. Furthermore, Hazan et al. teaches that the peptide is phosphorylated on the second tyrosine (y1222) in analogy with the EGF receptor (p. 4, end of col. 1, and Figs. 2 and 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 7, 9-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dobrusin et al (WO94/07913).

Dobrusin et al. is relied upon as discussed above. Also taught is that the peptide sequences disclosed may be modified by replacing the phosphotyrosine by a mimic such as (phosphonomethyl)phenylalanine (p. 7, second paragraph). Dobrusin et al. does not specifically teach SEQ ID NO:7 substituted with a phosphotyrosine mimic.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute SEQ ID NO:7 and any other of the Dobrusin et al. peptides with a (phosphonomethyl)phenylalanine because it was well known and discussed by Dobrusin et al. that peptide/protein use is dependent on tyrosine phosphorylation. One would have been motivated to make the phosphotyrosine moiety more stable and non-hydrolyzable by substituting it with the (phosphonomethyl)phenylalanine analog. Also taught is a method of determining if a protein comprises a PTB domain by contacting the protein with a peptide and determining binding wherein the peptide was fused to a detectable label (S^{35}) and bound to protein A-Sepharose beads in a column (a solid support, p. 17, lines 15-30). Additionally the peptides of Dobrusin et al. were used to determine if a test compound was an agonist or antagonist of a PTB/phosphorylated ligand interaction (p. 17-18, *e.g.*, Fig. 3).

It would have been obvious to perform the methods of Dobrusin using SEQ ID NO:7 or any one of the peptides taught to determine their interaction with a PTB domain for the reasons taught by Dobrusin because it is stated (p. 15, lines 14-19) that, "The compounds of Formula I [including SEQ ID NO:7] are valuable inhibitors of the association of a tyrosine kinase with its cellular substrates and effectively uncouple the tyrosine kinase from specific signal transduction pathway(s)." It is suggested that inhibition of this binding can inhibit some hyperproliferative diseases like cancer (p. 5, second paragraph).

Claims 13-16 are rejected under 35 USC 103 as being unpatentable over Dobrusin et al (WO94/07913) in view of Pawson (US Patent 5,352,660)) and Blaikie et al. (J. Biol. Chem., 269 (51):32031-32034 (1994)).

Dobrusin discloses a peptide (SEQ ID No.7) containing the sequence ENAEpYL which meets the limitation given for the core sequence. Claims 1, 2 and 3 of the instant application are to peptides having a core sequence NX3X1X2X4, which is capable of binding a PTB domain, and SEQ ID NO:7 of Dobrusin et al. has the required structure. Claim 9 is directed to a composition comprising the peptide of claim 1 in a pharmaceutically acceptable carrier. Dobrusin teaches pharmaceutical compositions including compounds of their invention, which include the peptides of instant claim 1 (pages 15-16). Dobrusin teaches that the sequence of the peptides disclosed are derived from sequences in tyrosine kinase receptors, including erbB2/neu, that include phosphotyrosine and bind other SH2 containing proteins. Dobrusin et al. do not teach SHC comprising a PTB domain

Pawson teaches a method of identifying substances that affect the binding of a phosphorylated ligand to a SH2 domain containing protein. The phosphorylated ligand is defined as a polypeptide or peptide that contains phosphotyrosine and is capable of interacting with a SH2 domain (col. 7, line 46+). The phosphorylated peptide and the Sh2 domain-containing protein are then incubated in the presence and absence of a test

compound, and amounts of complexed and free phosphorylated peptide and SH2 domain-containing protein are assayed to determine changes in binding.

Blaikie discloses that SHC has a novel phosphotyrosine binding domain (PTB) that is able to interact with the c-erbB-2/neu receptor.

It would have been obvious to one of ordinary skill in the art at the time of Applicant's invention, to modify the method of Pawson et al. to use the novel phosphotyrosine binding domain of Blaikie and the phosphopeptide of Dobrusin, to identify compounds that affect the binding of the peptide ligand to the SHC binding domain. One would have been motivated to do so, to identify domains involved in signal transduction and design drugs for treatment of diseases where signal transduction is improper. One would have had reasonable expectation of success because of Dobrusin teachings.

Claims 10-13 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlessinger et al.(WO92/13001) in view of Dobrusin et al. (WO94/07913) and Blaikie et al. Blaikie et al. (J. Biol. Chem., (1994)).

Schlessinger et al. teach a method for the identification of proteins that bind to the carboxy terminal region of tyrosine kinase receptors such as the epidermal growth factor receptor. The method comprises attaching proteins from an expression library to a solid support such as nitrocellulose filters (page 16, lines 20-23), and contacting the proteins with probes that are peptides derived from the C-terminal tail of the EGF receptor (page 13, lines 4-10) or the HER2/neu receptor (page 14, line 10) followed by determination of binding by detection of labeled probe (page 5, lines 21-23). They teach that the peptide may be radioactively labeled (page 5, line 32). The peptide might be attached to a solid phase carrier matrix (page 20, line 35 to page 21, line 7), thus creating an affinity probe than can be used to isolate and purify molecules from complex mixtures which are capable of binding to the affinity probe, or to detect the presence of agents able to interact with the probe. They teach the synthesis of phosphorylated polypeptides (page

17, second paragraph, and page 26, lines 16-26). They do not teach the specific peptide of claim 10.

Blaikie teaches the binding of the amino terminal residues of Shc to EGF, neu and TrkA receptors.

Dobrusin also teaches (Table I, SEQ ID No.7), a 14 amino acid long peptide having a core sequence NAEpYL that meets the limitation of the peptide of claim 10.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Schlessinger et al. by using the peptides disclosed by Dobrusin and isolate other proteins that also contain the novel phosphotyrosine binding domain of Shc taught by Blaikie. One would have been motivated to do so because proteins or domains that bind to phosphotyrosines on growth factor receptors are important in the transmission of growth factor signals, and that the isolation of new proteins containing such domains or interacting with such peptides would be important mediators of the growth factor signaling pathway. One would have had reasonable expectation of success, because of the results of Blaikie and Dobrusin showing that different amino acid motifs containing a phosphotyrosine are able to bind to receptors having phosphotyrosine binding domains. It would further have been obvious to modify the method of Schlessinger and use the peptides of Dobrusin or Blaikie bound to solid support matrix, and isolate other proteins containing the phosphotyrosine binding domain that binds to this peptide, for the reasons cited above and because ligands bound to solid supports are well known in the art to be useful to isolate proteins that bind to them.

Conclusion

All references cited on the attached PTO-829 are present and cited in parent application 08/423,646, and so will not be provided again.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

September 25, 2003